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Synthesis of allyl ketone via Lewis acid promoted Barbier-type reaction

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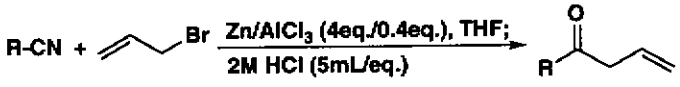
Abstract

A series of allyl ketones were synthesized from the mixture of zinc, nitrile and allyl bromide in the presence of $AlCl_3$ via Barbier-type reaction condition. When crotyl bromide was used for the allylation, only the γ-adduct was produced via the S_E2' pathway under the reaction condition.

Since Blaise reported the addition of allylic iodide to nitrile, this potentially useful β,γ-unsaturated ketone synthesis found little application in organic synthesis.[1] Despite the notable successes of allylation of carbonyl compounds,[2,3] the condensation of allylic organometal derivatives with nitriles for the direct synthesis of β,γ-unsaturated ketones have usually to be prepared indirectly by long and tedious methods and low yields are generally observed.[4–6] Allyl ketones have been prepared by the reactions of allyl organometallics of antimony,[7] cadium,[8] copper,[9] indium,[10] manganese,[11] mercurry,[12] nickle,[13] rhodium,[14] silicon,[15,16] tin[17,18] and zinc[19] with acyl halides, but little functionality can be accommodated by these processes. Our previous studies showed that β-amino-α,β-unsaturated ester was generated by a sonochemical Blaise reaction condition.[20,21] Therefore, we further investigated the allylation of allyl organometal compounds (e.g. Bi, In, Li, Mg, Zn) with nitrile under the Barbier-type reaction condition. Herewith, we wish to report an improvement in the Barbier-type allylation of nitrile in the presence of Lewis acid which leads to the synthesis of allyl ketone after acidic quenching (Scheme 1).



Scheme 1.

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The typical procedure for the synthesis of allylketone is as follows: aluminum trichloride (0.4 mmol) was added at once to a solution of zinc powder (4.0 mmol), nitrile (1.0 mmol) and allylic bromide (1.5 mmol) in anhydrous THF (5 mL) at 0°C (ice-water bath).[22] The reaction mixture was warmed to room temperature and then stirred at room temperature. After the reaction was completed (monitored by TLC), aqueous HCl (2 M, 5 mL) was added to the reaction mixture and stirred at room temperature for 5 minutes. The reaction mixture was passed through a short silica gel column and the organic solvent was removed directly under reduced pressure. Further purification is achieved on a flash chromatograph with ethyl acetate/hexane as eluant. A series of allyl ketones are synthesized under this typical reaction condition and the results are shown in Table 1.

Table 1
Synthesis of allyl ketones

Entry	Substrate	Product	Time(h)	Yield[a]
1	$CH_3CH_2CH_2CH_2$-CN	$CH_3CH_2CH_2CH_2$	2	58%[b]
2	$BrCH_2CH_2CH_2$-CN	$BrCH_2CH_2CH_2$	2	60%
3	CN		2	61%[b]
4	CH_2CN		2	78%
5	MeO_2C-CH_2-CN	MeO_2C	18	52%
6	CN		2	63%
7	CN		1.5	71%
8	CN		0.5	85%
9	CN		2	58%
10	CN	S	2	60%

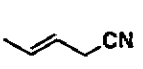
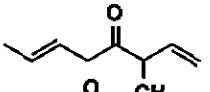
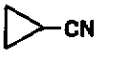
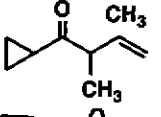
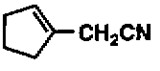
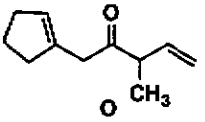
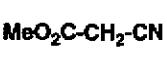
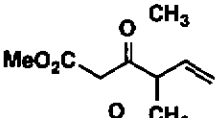
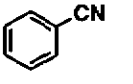
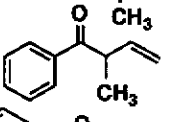
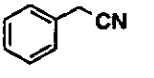
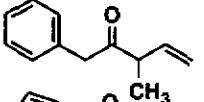
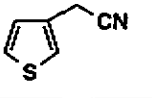
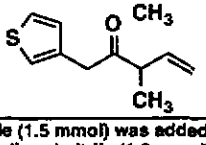
(a) The yields were determined after chromatographic purification.
(b) The yield is low because the product is highly volatile.

According to our previous studies for the activation of zinc by using ultrasound, we first investigated the reaction of allylic bromide with benzylnitrile under sonochemical Barbier-type reaction condition.[20,21,23] No expected allyl ketones were generated under the ultrasonic reaction condition. Thus, we investigated this sonochemical reaction condition in the presence of Lewis

acid such as $AlCl_3$, $BiCl_3$ and $CeCl_3$ for the activation of zinc and nitrile, but low yields were achieved. Interestingly, the yield of allyl ketone was improved when allylic bromide was added to a mixture of Zn, $AlCl_3$ and nitrile in THF without ultrasound as activation source for zinc metal. We also observed that the addition of Lewis acid to the mixture of zinc powder, nitrile and allylic bromide in anhydrous THF increased dramatically the yield of allyl ketone. Many Lewis acids such as $TiCl_4$, $ZrCl_4$, $SnCl_4$, $AlCl_3$, $BiCl_3$, $CeCl_3$, BF_3 and $ZnCl_2$ were investigated and the $AlCl_3$ and $ZrCl_4$ are the best Lewis acids for the allylation reaction with nitrile. Alkyl and aryl nitriles were reacted with allylic bromide in the presence of $AlCl_3$ to produce corresponding allyl ketones with moderate to high yields under the reaction conditions.

Studies on the reactions of substituted allylmetals with carbonyl compounds were carried out which focused on the regioselectivity of the allylic unit (S_E2 or S_E2'). Therefore, we further investigated the regioselectivity of the allylation reaction with nitrile under the reaction condition. A mixture of zinc powder (4.0 equiv.), $AlCl_3$ (0.4 equiv.), crotyl bromide (1.5 equiv.) and benzyl nitrile (1.0 equiv.) in THF was investigated under the reaction condition and a 36% yield of 2-methyl allyl ketone (γ-adduct) was obtained after chromatography. We found that when the crotyl bromide (1.5 equiv.) was added dropwise to a mixture of Zn powder (3.0 equiv.), $AlCl_3$ (0.3 equiv.) and benzyl nitrile (1.0 equiv.) a higher yield (77%) was obtained. The lower amount of Zn and $AlCl_3$ and a different addition order of crotyl bromide improved the yield of 2-substituted allyl ketone. A series of 2-methyl allyl ketones were synthesized under this reaction condition and the results are shown in Table 2.

Table 2
Synthesis of 2-methyl allyl ketones[a]

Entry	Substrate	Product	Yield[b]
1			60%
2			53%[c]
3			57%
4			39%
5			72%
6			77%
7			71%

(a) The typical procedure: crotyl bromide (1.5 mmol) was added dropwise to a mixture of Zn (3.0 mmol), $AlCl_3$ (0.3 mmol) and nitrile (1.0 mmol) in THF (5 mL) in water bath at room temperature. After the reaction was completed, aqueous HCl (5 mL) was added and the reaction mixture was stirred at r.t. for 5 minutes.
(b) The yields were determined after chromatographic purification.
(c) The yield is low because the product is highly volatile.

In conclusion, this Lewis acid promoted Barbier-type reaction condition provides a simple and facile method for the synthesis of allyl ketones. All nitriles and allylic bromides were used directly without further purification when they were received. This procedure features in situ activation of metal to generate allylmetal which reacted with nitrile to form allyl ketone after acidic quenching. In addition, our investigations showed that numerous functionalities were also inert to this reaction condition (e.g. bromide, ester, heterocyclic, etc.). These results led us to expand this Lewis acid promoted Barbier-type reaction for synthesis of other biological compounds.

Acknowledgements

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